REMARKS

Revocation and New Power of Attorney & Change of Correspondence Address

Applicants include a Power of Attorney and Correspondence Indication Form and a Statement under 37 C.F.R. §3.73(b) both signed by Gustave J. Bernhardt, as Director, Research Resources Management of the Assignee, Sloan-Kettering Institute for Cancer Research and appoints the undersigned to prosecute the above-referenced patent application before the U.S. Patent and Trademark Office.

Status of the Claims

Claims 1, 2, 4-49 and 51-61 are pending. Claims 1, 2, 4, 5, 7-17, 19-25, 27-36, 38-43, 45-49, 51, 52 and 55-61 are rejected. Claims 6, 18, 26, 37, 44, 53 and 54 are objected to.

Claim 1, 2, 4, 5, 13, 14, 15, 18, 26, 32, 33, 34, 37, 38, 40, 44, 49, 52, 53 and 57 are amended and claims 3, 6, 16-17, 35-36, 50 and 54 are canceled herein. No new matter is added to these claims.

Claim amendments

Independent claims 1, 13, 32 and 49 are amended to overcome the 35 U.S.C. §103(a) rejections. The method of reducing nephrotoxicity during radioimmunotherapeutic treatment as claimed in amended claim 1 comprises administering a pharmacologically effective dose of a competitive metal blocker

consisting of bismuth subnitrate or bismuth subcitrate either alone or in combination with one or both of a chelator(s) or a diuretic(s) and administering an actinium-225 radioimmunoconjugate to treat the pathophysiological condition. This instantly claimed method is supported by the demonstration of prevention of accumulation of alpha-particle emitting daughters of actinium-225 using chelators, diuretics and competitive metal blockers or combinations thereof in Examples 5, 6, 7, 8, 9 of the instant invention.

Additionally, the method of reducing nephrotoxicity during radioimmunotherapeutic treatment as claimed in amended claim 13 comprises administering a pharmacologically effective dose of a diuretic in combination with a chelator and administering an actinium-225 radioimmunoconjugate to treat the cancer. The instantly claimed method is supported by Example 6 of the instant invention that teaches that a diuretic therapy either alone or in combination with chelator was effective in preventing accumulation of bismuth-213 daughters and francium-211 daughters of actinium-225.

Further, the method of improving radioimmunotherapeutic treatment of cancer as claimed in amended claim 32 comprises administering a pharmacologically effective dose of a diuretic and a chelator; administering an actinium-225 radioimmunoconjugate and preventing accumulation of bismuth-213 daughters and francium-211 daughters of the actinium-225, thereby increasing the therapeutic index of the actinium-225 to improve the treatment for the cancer. As discussed supra, this method is supported by the teachings in Example 6 of the instant invention.

Furthermore, the method of increasing the therapeutic index of an actinium-225 radioimmunoconjugate as claimed in amended claim 49 comprises inhibiting renal uptake of at least one alpha particle-emitting daughter of actinium-225 which comprises administering a pharmacologically effective amount of one or both of a diuretic or a competitive metal blocker consisting of bismuth subnitrate or bismuth subcitrate or one or both of the diuretic or the competitive metal blocker in combination with a chelator. As discussed supra, the teachings of the instant claim 49 is supported by the teachings in Examples 5, 6, 7, 8, 9 of the instant invention.

Claims 2, 14, 33, 38 and 40 are amended to properly depend from their respective independent claims. Additionally, claims 4, 15, 34 and 52 are amended to correct the claim language and include chelators such as dithiol chelating agent, 2,3 dimercapto-1-propane sulfonic acid, meso 2, 3-dimercapto succinic acid and diethylenetriamine pentaacetic acid. The inclusion of these chelators in these claims is supported by the teachings in the instant specification (page 18, line 19-page 19, line 5).

The 35 U.S.C. §112, First Paragraph Rejection

Claims 1, 2, 7-14, 16-17, 19-25, 27-33, 35-36, 38-43, 45-49, 51 and 55-61 remain rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. Applicant respectfully traverses this rejection.

The Examiner states that while the claims recite the three sub-genuses of molecules, i.e., a chelator, a diuretic, a competitive metal blocker and a function, e.g., preventing accumulation of alpha-particle emitting daughters, the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "adjuvant and/or chelator, diuretic or competitive metal blocker" are not set forth in the specification as filed. Accordingly, the Examiner states that since there is insufficient written description encompassing any "adjuvant and/or chelator, diuretic or competitive metal blocker effective for preventing accumulation of a metal in a kidney", the written description provided by Applicants' specification is not commensurate in scope with the broad subgenuses claimed. Applicant respectfully disagrees.

The instant claims 1 and 49 are amended herein to recite the names of specific competitive metal blockers. The instantly claimed methods are drawn to preventing accumulation of actinium-225 and its daughters, bismuth-213 and francium-221 in the kidneys of an individual undergoing radioimmunotherapeutic treatments (Examples 5-9). In this regard, the instant invention disclosed that chelators such as DMPS or DMSA were capable of chelating Bi-213 and diuretics such as furosemide and chlorthiazide inhibited renal tubular reabsorption of Fr-221. Additionally, the instant invention also discloses that the combination of a chelator (DMPS) and a diuretic (furosemide or chlorthiazide resulted in an even greater reduction in renal Bi-213 activity. Furthermore, the instant invention discloses that a competitive blockade of Bi-213 binding sites in the renal tubular cells by non-radioactive bismuth (bismuth

subnitrate) resulted in a significant reduction in renal Bi-213 activity. Therefore, although there are various chelators or diuretics that are routinely used in the art, the instant specification provides a description of the chelators or diuretics that useful in the claimed methods by using representative examples. In addition, since chelators and diuretics are routinely being used in the art, their physical and chemical characteristics are also well-established. Therefore, based on the information disclosed in the instant specification along with the knowledge regarding the chelators and diuretics readily available in the art, Applicants respectfully submit that a person having ordinary skill in this art could easily recognize chelators and diuretics useful in the claimed methods.

Applicants respectfully note that not every embodiment of the claimed invention has to be demonstrated if the information in the specification is sufficiently detailed to allow a person having ordinary skill in the art to practice the claimed method without undue experimentation. As discussed supra, a fair reading of the instant specification and the knowledge available in the art regarding chelators and diuretics would allow a person having ordinary skill in the art to easily recognize useful chelators or diuretics to practice the claimed invention. Applicants respectfully submit that a person having ordinary skill in this art could readily determine, without undue experimentation, which chelators or diuretics not taught in the instant specification would be useful to practice the claimed methods. The Examiner has not provided any scientific evidence to the contrary. Hence, Applicant submits that the written description is commensurate in scope with the sub-genuses claimed. In view of the claim amendments and

remarks, Applicant respectfully requests the withdrawal of rejection of claims 1, 2, 7-14, 16-17, 19-25, 27-33, 35-36, 38-43, 45-49, 51 and 55-61 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §103 Rejection

Claims 1-2, 4, 7-8, 10-11, 13-15, 19, 32-34, 49, 51-52, 55 and 58-60 remain rejected under 35 U.S.C. §103(a) as being unpatentable over **Kennel** *et al* (Cancer Biotherapy & Radiopharmaceuticals, 15:235-244, 2000) in further view of **Jones** *et al* (Nuclear Medicine & Biology, 23: 105-113, 1996). Applicant respectfully traverses this rejection.

The Examiner states that **Kennel** *et al* teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate, wherein the radiotoxicity associated with 213Bi accumulation in the kidneys limits the effectiveness of the therapy, while **Jones** *et al* teach that DMPS accelerated the body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Based on this data, the Examiner states that one of ordinary skill in the art would have reasonable expectation of success that by administering an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope bound to a HEHA-MAb 201B conjugate, one would reduce the accumulation of ^{213}Bi in the kidney. Applicant respectfully disagrees.

Kennel *et al* evaluated Ac-225 for vascular targeted radioimmunotherapy and teach that the potential for Ac-225 as

radioimmunotherapeutic agent is compromised most importantly by the radiotoxicity associated with the decay daughter radioisotopes released from the target organ (Abstract). **Kennel** *et al* further teach lack of a conventional chelate that could withstand the energy released by radioactive decay of Ac-225 (page 243, 1st col., lines 2-4). **Jones** *et al* teach that DMPS can be used as a potential adjuvant chelation therapy in Lead-212 or Bismuth-212 radioimmunotherapy protocols (Abstract). Assuming *arguedo* that this combination of prior art references suggest or teach using dithiol chelating agents as potential adjuvant in Ac-225 radioimmunotherapy, the combination of **Kennel** *et al* and **Jones** *et al* neither teach nor suggest combining the dithiol chelating agents with any other adjuvants to reduce the toxicity associated with Ac-225 associated radioimmunotherapy.

In contrast, Applicants' amended claims recite the use of a diuretic and/or competitive metal blocker such as bismuth subnitrate or bismuth subcitrate in combination with chelators in the Ac-225 radioimmunotherapy treatments. Specifically, instant claims 1 and 13 drawn to method of reducing nephrotoxicity during radioimmunotherapy recites the use of a competitive metal blocker either alone or in combination with chelators and/or diuretics and the use of a diuretic in combination with a chelator, respectively. Further, claim 32 drawn to method of improving radioimmunotherapy recites the use of a diuretic and a chelator while claim 49 drawn to increasing the therapeutic index of AC-225 radioimmunoconjugate recites the use of a diuretic and/or a competitive metal blocker in combination with a chelator. As there is no such teaching, motivation

or suggestion in the combination of these two prior art references, these references combined do not fairly teach or suggest all the claimed invention.

In view of this, Applicant submits that claims 1-2, 4, 7-8, 10-11, 13-15, 19, 32-34, 49, 51-52, 55 and 58-60 are not prima facie obvious over the combined teachings of the prior art references. Accordingly, based on the claim amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 1-2, 4, 7-8, 10-11, 13-15, 19, 32-34, 49, 51-52, 55 and 58-60 under 35 U.S.C. §103(a).

Claims 1-2, 4, 7-15, 19-23, 32-34, 49, 51-52, 55 and 58-61 remain rejected under 35 U.S.C. §103(a) as being unpatentable over **Scheinberg** *et al* (US 2002/0058007, 2002) in further view of **Jones** *et al* (Nuclear Medicine & Biology, 23: 105-113, 1996). Applicant respectfully traverses this rejection.

The Examiner states that **Scheinberg** *et al* teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (pg. 2, para. 0016) such that internalization of the ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi (pg. 2, para 0017). With regards to **Jones** *et al*, the Examiner states that this prior art reference teaches that dithiol agents such as 2, 3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2, 3-dimercaptosuccinic acid (DMSA) reduce or prevent radiotoxicity of Lead-212 or Bismuth-212 alpha-radioimmunotherapy by demonstrating an accelerated body clearance of bismuth

and dramatically reduced early and late accumulation of bismuth in the kidney on administration of DMPS (pg. 112, 2nd col, conclusion).

Based on this, the Examiner states that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer an adjuvant such as 2, 3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate as taught by **Scheinberg** *et al* in view of **Jones** *et al* teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, the Examiner states that one of ordinary skill in the art would have a reasonable expectation of success in achieving a method for reducing the accumulation of ^{213}Bi in the kidney by administering an adjuvant such as 2, 3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate to an individual, which in turn would reduce the nephrotoxicity in the individual. Applicant respectfully disagrees with the Examiner.

Scheinberg *et al* teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an Ac-225 conjugate comprising a functionalized chelate where internalization of Ac-225 permits emission of alpha particles or its daughters, which accumulates in the kidney (Example 9). The teachings of **Jones** *et al* are as discussed supra by the Applicant. Accordingly, the prior art references combined suggest or teach using dithiol chelating agents as potential adjuvant in Ac-225 radioimmunotherapy and neither teach nor suggest combining the dithiol chelating agents with any other

adjuvants to reduce the toxicity associated with Ac-225 associated radioimmunotherapy.

In contrast, the instantly claimed methods recite the use of a diuretic and/or a competitive metal blocker such as bismuth subnitrate or bismuth subcitrate in combination with chelators in the Ac-225 radioimmunotherapy treatments. Specifically, instant claims 1 and 13 drawn to method of reducing nephrotoxicity during radioimmunotherapy recites the use of a competitive metal blocker either alone or in combination with chelators and/or diuretics and the use of a diuretic in combination with a chelator, respectively. Further, claim 32 drawn to method of improving radioimmunotherapy recites the use of a diuretic and a chelator while claim 49 drawn to increasing the therapeutic index of Ac-225 radioimmunoconjugate recites the use of a diuretic and/or a competitive metal blocker in combination with a chelator. Since there is no such teaching or suggestion in the prior art references combined, these references combined do not fairly teach or suggest all the limitations of the claimed invention. For the same reason, one of ordinary skill in the art would not be motivated to combine the teachings of the prior art references.

Even if a person having ordinary skill in this art were motivated to combine the teachings of these prior art references, one would not be able to arrive at the instant claims with a reasonable expectation of success absent the teachings of the instant invention. In view of this, Applicant submits that the independent claims 1, 13, 32 and 49 and their dependent claims are not prima facie obvious over the combined teachings of the prior art references.

Accordingly, based on the claim amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 1-2, 4, 7-15, 19-23, 32-34, 49, 51-52, 55 and 58-61 under 35 U.S.C. §103(a).

Claims 5 and 53 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Scheinberg** *et al* (US 2002/0058007, 2002) and **Jones** *et al* (Nuclear Medicine & Biology, 23: 105-113, 1996) in further view of **Schilcher** *et al* (J Can Res Clin Oncol, 107: 57-60, 1984). Applicant respectfully traverses this rejection.

The Examiner applies **Scheinberg** *et al* and **Jones** *et al* as discussed supra. Additionally, the Examiner states that **Schilcher** *et al* teach use of Furosemide, a diuretic for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract). Based on this, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer a diuretic such as furosemide in combination with an Ac-225 conjugate in view of the combined teachings of the prior art references. Additionally, the Examiner states that one would have been motivated to do so because **Jones** *et al* teach that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal binding proteins. Furthermore, the Examiner states that one of ordinary skill in the art would have a reasonable expectation of success in achieving reduction in the

accumulation of Bi-213 in the kidney or reduction of nephrotoxicity by administering a diuretic such as furosemide in combination with an Ac-225 conjugate comprising a functionalized chelate. Applicant respectfully disagrees.

The teachings of **Scheinberg** *et al* and **Jones** *et al* are discussed supra. **Schilcher** *et al* evaluated the effect of fractionated low and single high dose cisplatin in various tumors. In this regard, **Schilcher** *et al* teach that cisplatin therapy was associated with nephrotoxicity (page 59, col. 2, 3rd para). Other than merely stating that cumulative nephrotoxicity could be prevented by treatment with furosemide, **Schilcher** *et al* do not support this assertion with any actual data. In fact, even the nephrotoxicity associated with the cisplatin therapy was observed in a statistically insignificant number of patients. Moreover, the cisplatin-induced damage of the kidney cells is different and distinct from the damage induced by daughters of actinium-225. Therefore, a person having ordinary skill in this art would not know if furosemide would prevent the nephrotoxicity of actinium-225 radioimmunotherapy by absorbing daughters of actinium-225 simply based on the the extremely limited disclosure of **Schilcher** *et al*. In view of this, the prior art references combined neither teach nor suggest using a competitive metal blocker either alone or with one or both of a chelator or a diuretic.

In contrast, the instant invention teaches methods of reducing nephrotoxicity associated with Ac-225 radioimmunotherapy. Accordingly, instant claim 1 drawn to method of reducing nephrotoxicity during radioimmunotherapy recites the use of a competitive metal blocker either alone or in combination with chelators and/or diuretics. Further, claim 49 drawn to increasing the therapeutic

index of Ac-225 radioimmunoconjugate recites the use of a diuretic and/or a competitive metal blocker in combination with a chelator. Since there is no teaching or suggestion in the prior art references combined to use a competitive metal blocker alone or in combination with one or both of chelator or diuretic, the prior art references combined do not fairly teach or suggest all the limitations of claim 1 and claim 49. For the same reason, one of ordinary skill in the art would not be motivated to combine the teachings of the prior art references to arrive at the instant claims.

In view of this, Applicant submits that the claims 5 and 53 are not prima facie obvious over the combined teachings of the prior art references. Accordingly, based on the claim amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 5 and 53 under 35 U.S.C. §103(a).

Claims 1-2, 4, 7-15, 19-23, 32-34, 49, 51-52, 55 and 58-61 are rejected under 35 U.S.C. §103(a) as being unpatentable over **McDevitt** *et al* (Science, 294: 1537-1540, 2001) in further view of **Jones** *et al* (Nuclear Medicine & Biology, 23: 105-113, 1996). Applicant respectfully traverses this rejection.

In the instant case, the Examiner states that **McDevitt** *et al* teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi accumulation in the kidney as a result of the decay of the daughters from non-targeted constructs, while **Jones** *et al* teach that DMPS

accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Hence, the Examiner states that one of ordinary skill in the art would have reasonable expectation of success that by administering to an adjuvant such as 2, 3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope immunoconjugate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney. Applicant respectfully disagrees.

The teachings of **Jones** *et al* are discussed supra. **McDevitt** *et al* examined tumor therapy with targeted atomic nanogenerators. In this regard, **McDevitt** *et al* teach that Ac-225 can be used as a safe and potent tumor-selective molecular-sized generator in both established solid carcinomas or disseminated cancers. Additionally, **McDevitt** *et al* also teach that the daughters of Ac-225 might be transferred to other sites such as the kidneys and intestine (pg. 1538, col.2, line 14-col.3, line 5). Thus, the prior art references combined teach or suggest using a chelator in combination with the Ac-225 radioimmunotherapy and neither teach nor suggest combining the dithiol chelating agents with any other adjuvants to reduce the toxicity associated with Ac-225 associated radioimmunotherapy.

In contrast, the instantly claimed methods recite the use of a diuretic and/or competitive metal blocker such as bismuth subnitrate or bismuth subcitrate in combination with chelators in the Ac-225 radioimmunotherapy treatments. Specifically, instant claims 1 and 13 drawn to method of reducing nephrotoxicity during radioimmunotherapy recites the use of a competitive metal blocker either alone or in combination with one or both of chelators or diuretics

and the use of a diuretic in combination with a chelator, respectively. Further, claim 32 drawn to method of improving radioimmunotherapy recites the use of a diuretic and a chelator while claim 49 drawn to increasing the therapeutic index of Ac-225 radioimmunoconjugate recites the use of one or both of a diuretic or a competitive metal blocker alone or in combination with a chelator. Since there is no such teaching or suggestion in the prior art references combined, these references combined do not fairly teach or suggest all the limitations of the claimed invention. For the same reasons, one of ordinary skill in the art would not be motivated to combine the teachings of the prior art references.

Even if one of skill in the art were motivated to combine the teachings of these prior art references, one would not be able to arrive at the instant claims with reasonable expectation of success absent teachings of the instant invention. In view of this, Applicant submits that claims 1, 13, 32 and 49 and their dependent claims are not prima facie obvious over the combined teachings of the prior art references. Accordingly, based on the claim amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 1-2, 4, 7-15, 19-23, 32-34, 49, 51-52, 55 and 58-61 under 35 U.S.C. §103(a).

Claim objections

Claims 6, 18, 26, 37, 44 and 53-54 are objected for being dependent from a rejected independent claim. Applicant respectfully traverses this rejection.

In view of the claim amendments and the discussions presented supra, claims 6, 18, 26, 37, 44 and 53-54 are no longer dependent from rejected independent claims . Accordingly, the objection of claims 6, 18, 26, 37, 44, 53 and 54 is moot.

This is intended to be a complete response to the Final Office Action mailed November 29, 2006. A Request for Continued Examination, a Petition for Extension of Time and Form PTO-2038 are also included with the response. Applicant submits that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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